```
=> s (muscarin? or (nicotin?(l)acetylcholine))(l)piperidin?
         27029 MUSCARIN?
         88368 NICOTIN?
         75825 ACETYLCHOLINE
         96504 PIPERIDIN?
L1         720 (MUSCARIN? OR (NICOTIN?(L)ACETYLCHOLINE))(L)PIPERIDIN?

=> s l1 and (piperidin?(l)phenoxy?)
         96504 PIPERIDIN?
         67416 PHENOXY?
          1698 PIPERIDIN?(L)PHENOXY?
L2          13 L1 AND (PIPERIDIN?(L)PHENOXY?)

=> d bib abs 1-13

L2   ANSWER 1 OF 13  CAPLUS  COPYRIGHT 2007 ACS on STN
AN   2005:700141  CAPLUS
DN   143:186601
TI   Phenoxybenzamine and benextramine, but not 4-diphenylacetoxy-N-
     [2-chloroethyl]piperidine hydrochloride, display irreversible
     noncompetitive antagonism at G protein-coupled receptors
AU   Bodenstein, Johannes; Venter, Daniel P.; Brink, Christian B.
CS   Division of Pharmacology, The Northwest University (PUK), Potchefstroom,
     S. Afr.
SO   Journal of Pharmacology and Experimental Therapeutics (2005), 314(2),
     891-905
     CODEN: JPETAB; ISSN: 0022-3565
PB   American Society for Pharmacology and Experimental Therapeutics
DT   Journal
LA   English
AB   Many irreversible antagonists have been shown to inactivate G
     protein-coupled receptors (GPCRs) and used to study agonists and spare
     receptors.  Presumably, they bind to primary (agonist) binding sites on
     the GPCR, although noncompetitive mechanisms of antagonism have been
     demonstrated but not thoroughly investigated.  The authors studied
     noncompetitive antagonism by phenoxybenzamine and benextramine
     at α2A-adrenoceptors in stably transfected Chinese hamster ovary
     cells, benextramine and 4-diphenylacetoxy-N-[2-chloroethyl]
     piperidine hydrochloride (4-DAMP mustard) at endogenous
     muscarinic acetylcholine (mACh) receptors in human neuroblastoma
     SH-SY5Y cells, and benextramine at serotonin 5-HT2A receptors in stably
     transfected SH-SY5Y cells.  Primary binding sites were protected by
     reversible competitive antagonists during pretreatment with irreversible
     antagonists.  The authors conducted appropriate radioligand binding assays
     by measuring remaining primary binding sites and agonist affinity,
     functional assays to evaluate agonist-induced responses, and constitutive
     guanosine 5'-O -(3-[35S]thio)triphosphate ([35S]GTPγS)-Gαo
     binding assays to determine remaining G protein activity.
     Phenoxybenzamine (100 μM; 20 min) and benextramine (10 or 100
     μM; 20 min) at α2A-adrenoceptors, but not 4-DAMP mustard (100 nM;
     120 min) at mACh receptors, displayed irreversible noncompetitive
     antagonism in addition to their known irreversible competitive antagonism.
     Although agonist binding affinity is not influenced, signal transduction
     is modulated in a G protein-dependent manner via allotopic interactions.
     Benextramine noncompetitively inhibits agonist-induced responses at three
     different GPCR types (α2A, mACh, and 5-HT2A receptors) that signal
     via three families of G proteins (Gi/o, Gs, and Gq/11).  The authors
     conclude that, where irreversible antagonists are utilized to study
     drug-receptor interaction mechanisms, the presence of significant
     irreversible noncompetitive antagonism may influence the interpretation of
     results under the exptl. conditions used.
```

RE.CNT 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:453812 CAPLUS
DN 143:7702
TI Preparation of biphenyl benzothiazole compounds having beta2 adrenergic receptor agonist and muscarinic receptor antagonist activity for treating pulmonary disorders
IN Mammen, Mathai; Dunham, Sarah
PA USA
SO U.S. Pat. Appl. Publ., 63 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2005113417	A1	20050526	US 2004-992927	20041119
	CA 2543858	A1	20050609	CA 2004-2543858	20041119
	WO 2005051946	A2	20050609	WO 2004-US38975	20041119
	WO 2005051946	A3	20050714		
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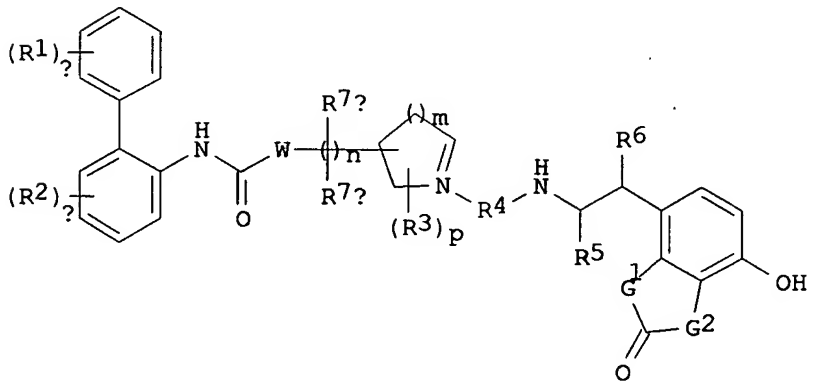
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1685118	A2	20060802	EP 2004-811663	20041119
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
	CN 1882556	A	20061220	CN 2004-80034201	20041119
PRAI	US 2003-524234P	P	20031121		
	WO 2004-US38975	W	20041119		

OS MARPAT 143:7702
GI



I

AB The invention is directed to compds. of formula I, wherein R1, R2, R3, R4, R5, R6, R7a, R7b, W, G1, G2, a, b, c, d and m are as defined below, or a

pharmaceutically acceptable salt or solvate or stereoisomer thereof. The invention is also directed to pharmaceutical compns. comprising such compds.; methods of using such compds.; and process and intermediates for preparing such compds. The compds. of the invention possess both β2 adrenergic receptor agonist and muscarinic receptor antagonist activity. Such compds. are expected to be useful as therapeutic agents for treating pulmonary disorders. Certain compds. of this invention have also been found to possess affinity for dopamine D2 receptors. For I: one of G1 and G2 = NH and the other represents S, NH, O or CH2; W = O or NWa; where Wa = H or (1-4C)alkyl; each R1 = (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo, -OR1a, -C(O)OR1b, -SR1c, -S(O)R1d, -S(O)2R1e or -NR1fR1g; where each of R1a, R1b, R1c, R1d, R1e, R1f and R1g = H, (1-4C)alkyl or phenyl(1-4C)alkyl; each R2 = (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo, -OR2a, -C(O)OR2b, -SR2c, -S(O)R2d, -S(O)2R2e or -NR2fR2g; where each of R2a, R2b, R2c, R2d, R2e, R2f and R2g = H, (1-4C)alkyl or phenyl(1-4C)alkyl; each R3 = (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, cyano, halo, -OR3a, -C(O)OR3b, -SR3c, -S(O)R3d, -S(O)2R3e or -NR3fR3g; or two R3 groups are joined to form (1-3C)alkylene, (2-3C)alkenylene or oxiran-2,3-diyl; where each of R3a, R3b, R3c, R3d, R3e, R3f and R3g = H or (1-4C)alkyl; R4 represents a divalent hydrocarbon group containing from 4 to 28 carbon atoms and optionally containing from 1 to 10 heteroatoms selected independently from halo, O, N, and S, provided that the number of contiguous atoms in the shortest chain between the two nitrogen atoms to which R4 is attached is in the range of from 4 to 16; R5 = H or (1-4C)alkyl; R6 = H or OH; each R7a and R7b = H, (1-4C)alkyl, OH and F; a = 0-3; b = 0-3; c = 0-4; d = 0-5; and m = 0-3.

L2 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:74113 CAPLUS
DN 142:176696
TI Preparation of substituted 4-amino-1-benzylpiperidines as muscarinic M2 receptor antagonists
IN Mammen, Mathai; Wilson, Richard; Dunham, Sarah; Hughes, Adam; Husfeld, Craig; Ji, Yu-Hua; Li, Li; Mischki, Trevor; Stergiades, Ioanna; Oare, David
PA Theravance, Inc., USA
SO PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005007645	A1	20050127	WO 2004-US22264	20040709
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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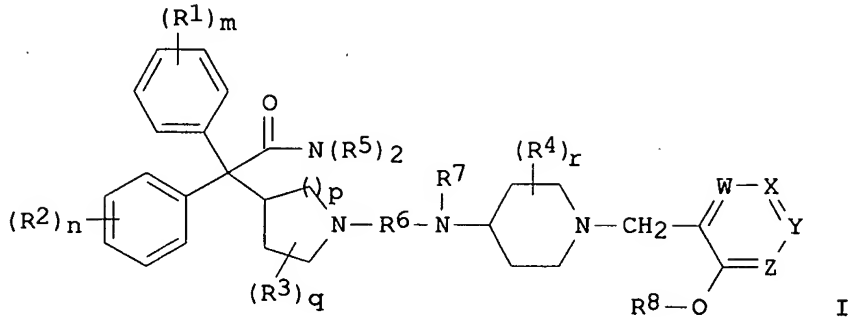
	US 2005026954	A1	20050203	US 2004-888855	20040709
	EP 1644356	A1	20060412	EP 2004-778013	20040709
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
PRAI	US 2003-486337P	P	20030711		
	WO 2004-US22264	W	20040709		

OS MARPAT 142:176696
GI



I

AB Title compds. I [W, X, Y, Z = CH, CR9; R6 = alkyloxyalkyl linker; R7-8 = H, alk(en/yn)yl, cycloalkyl, etc.; R9 = alk(en/yn)yl, cycloalkyl, etc.; R1-2 = alk(en/yn)yl, cycloalkyl, CN, etc.; R3-4 = alkyl, F; R5 = H, alk(en/yn)yl, cycloalkyl, aryl, etc.; m, n = 0-3; p = 1-2; q, r = 0-4] are prepared For instance, (S)-4-[N-[7-(3-(1-Carbamoyl-1,1-diphenylmethyl)pyrrolidin-1-yl)hept-1-yl]-N-(methyl)amino]-1-(2,6-dimethoxybenzyl)piperidine is prepared by reaction of [1-(2,6-Dimethoxybenzyl)piperidin-4-yl]methylamine and (S)-3-(1-carbamoyl-1,1-diphenylmethyl)-1-(7-oxohept-1-yl)pyrrolidine (MeOH, NaCNBH3) in 4% yield as a lyophilized colorless solid. I are muscarinic M2 receptor antagonists with Ki < 100 nM. I are useful for the treatment of disease conditions mediated by muscarinic receptors, such as overactive bladder, irritable bowel syndrome, asthma and chronic obstructive pulmonary disease.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:703125 CAPLUS
DN 141:225161
TI Preparation of biphenyl derivatives as β2-adrenergic agonists and muscarinic antagonists for pulmonary disorders.
IN Mammen, Mathai; Dunham, Sarah; Hughes, Adam; Lee, Tae Weon; Husfeld, Cralg; Stangeland, Eric
PA Theravance, Inc., USA
SO U.S. Pat. Appl. Publ., 85 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004167167	A1	20040826	US 2004-779157	20040213
	US 7141671	B2	20061128		
	AU 2004213411	A1	20040902	AU 2004-213411	20040213
	CA 2515777	A1	20040902	CA 2004-2515777	20040213
	WO 2004074276	A1	20040902	WO 2004-US4224	20040213
	WO 2004074276	B1	20041007		

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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,

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            MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
            GQ, GW, ML, MR, NE, SN, TD, TG
      WO 2004074812          A2     20040902    WO 2004-US4273          20040213
      WO 2004074812          A3     20041104
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              GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
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          RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
              BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
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              GQ, GW, ML, MR, NE, SN, TD, TG
      WO 2004074246          A2     20040902    WO 2004-US4449          20040213
      WO 2004074246          A3     20041118
          W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
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              MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
              GQ, GW, ML, MR, NE, SN, TD, TG
      US 2004209915          A1     20041021    US 2004-778290          20040213
      US 2004209860          A1     20041021    US 2004-778649          20040213
      EP 1592685             A1     20051109    EP 2004-711137          20040213
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      EP 1594860             A2     20051116    EP 2004-711117          20040213
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      EP 1615889             A2     20060118    EP 2004-711253          20040213
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              IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
      BR 2004007508          A      20060214    BR 2004-7508            20040213
      CN 1759108             A      20060412    CN 2004-80006528        20040213
      JP 2006517971          T      20060803    JP 2006-503544          20040213
      JP 2006517978          T      20060803    JP 2006-503604          20040213
      JP 2006518739          T      20060817    JP 2006-503553          20040213
      IN 2005DN03375         A      20070119    IN 2005-DN3375          20050728
      NO 2005004206          A      20051019    NO 2005-4206            20050909
      US 2006223858          A1     20061005    US 2006-448293          20060607
      US 2006223859          A1     20061005    US 2006-448294          20060607
      US 2006223860          A1     20061005    US 2006-448317          20060607
      US 2006229334          A1     20061012    US 2006-449004          20060607
      US 2007037984          A1     20070215    US 2006-582885          20061018
PRAI  US 2003-447843P        P      20030214
      US 2003-467035P        P      20030501
      US 2004-779157         A1     20040213
      WO 2004-US4224         W      20040213
      WO 2004-US4273         W      20040213
      WO 2004-US4449         W      20040213
OS    MARPAT 141:225161
GI
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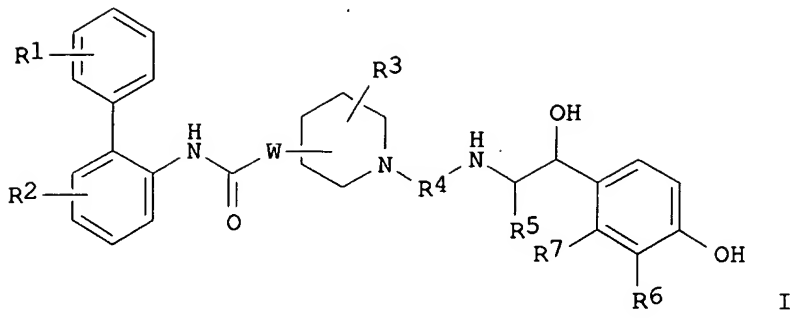

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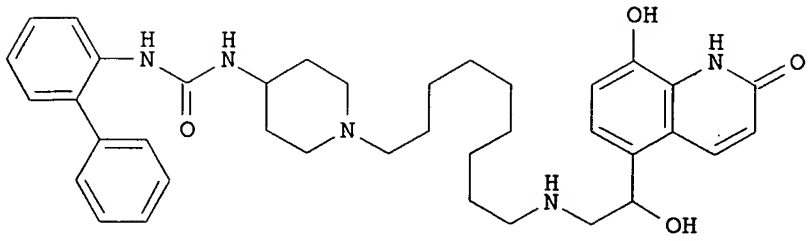

II

AB Title compds. I [R1 (taken 0-3 times) = alk(en/yn)yl, cycloalkyl, etc.; R2 (taken 0-3 times) = alk(en/yn)yl, cycloalkyl, CN, etc.; W = O, substituted N; R3 (taken 0-4 times) = alk(en/yn)yl, cycloalkyl, etc.; R4 = divalent group; R5 = H, alkyl; R6 = amino, alkoxy, etc.; R7 = H, etc.] are prepared For instance, N-[1,1'-Biphenyl-2-yl]-N'-[1-(9-aminononyl)piperidin -4-yl]urea (preparation given) is combined with 8-Benzyloxy-5-(2,2-dihydroxyacetyl)-1H-quinolin-2-one (CH2Cl2, NaHB(OAc)3) and the product reduced (MeOH, H2-Pd/C) to give II. Selected example compds. have Ki < 10 nM for the β2 and muscarinic receptor. I are useful in the treatment of pulmonary disorders, such as chronic obstructive pulmonary disease and asthma.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:982609 CAPLUS
DN 139:30159
TI Piperidine-containing histamine H3 receptor antagonists of the carbamate series: the influence of the additional ether functionality
AU Lazewska, D.; Kiec-Kononowicz, K.; Pertz, H. H.; Elz, S.; Stark, H.; Schunack, W.
CS Dep. Chem. Technology Drugs, Jagiellonian Univ., Krakow, Pol.
SO Pharmazie (2002), 57(12), 791-795
CODEN: PHARAT; ISSN: 0031-7144
PB Govi-Verlag Pharmazeutischer Verlag GmbH
DT Journal
LA English
AB Recently novel leads for histamine H3 receptor antagonists of the non-imidazole type have been described. As a continuation of this research eleven new carbamate derivs. possessing an addnl. ether functionality were prepared The compds. were evaluated in vitro for their antagonist activity on isolated organs of guinea-pig (GP) H3 as well as H2, H1, and M3 receptors, resp. All compds. investigated possessed moderate antagonist affinities at guinea-pig histamine H3 receptors (pA2 6.11-6.76). An ether functionality introduced in different places of the

lipophilic part of carbamnates differently influenced activity and selectivity toward H3, M3, and other histamine receptors tested.
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:798225 CAPLUS
DN 135:344471
TI Preparation of diazabicyclic compounds as central nervous system active agents
IN Schrimpf, Michael R.; Tietje, Karin R.; Toupence, Richard B.; Ji, Jianguo; Basha, Anwer; Bunnelle, William H.; Daanen, Jerome F.; Pace, Jennifer M.; Sippy, Kevin B.
PA Abbott Laboratories, USA
SO PCT Int. Appl., 190 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001081347	A2	20011101	WO 2001-US13798	20010427
	WO 2001081347	A3	20020131		
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2002019388	A1	20020214	US 2001-833914	20010412
	US 6809105	B2	20041026		
	CA 2407094	A1	20011101	CA 2001-2407094	20010427
	BR 2001007246	A	20021001	BR 2001-7246	20010427
	EP 1284976	A2	20030226	EP 2001-944118	20010427
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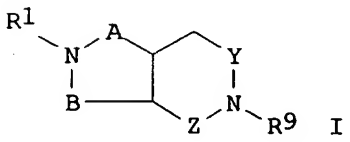
	HU 200300602	A2	20030628	HU 2003-602	20010427
	JP 2003531210	T	20031021	JP 2001-578437	20010427
	NZ 521734	A	20041029	NZ 2001-521734	20010427
	CN 1765899	A	20060503	CN 2005-10077862	20010427
	ZA 2002008274	A	20040211	ZA 2002-8274	20021014
	IN 2002MN01444	A	20050304	IN 2002-MN1444	20021017
	NO 2002005107	A	20021219	NO 2002-5107	20021024
	BG 107303	A	20030731	BG 2002-107303	20021121
	US 2004186107	A1	20040923	US 2004-810999	20040326
PRAI	US 2000-200111P	P	20000427		
	US 2000-559943	A	20000427		
	US 2001-833914	A	20010412		
	CN 2001-811711	A3	20010427		
	WO 2001-US13798	W	20010427		

OS MARPAT 135:344471
GI



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AB Diazabicyclic compds. (I; e.g. cis-2-(3-pyridinyl)octahydropyrrolo[3,4-c]pyrrole dihydrochloride), pharmaceutical compns. of these compds., and use of said compns. to control synaptic transmission in mammals are claimed. In I: A = covalent bond, CH2, CH2CH2, and CH2CH2CH2; B = CH2 and CH2CH2, provided that when A is CH2CH2CH2, then B is CH2; Y = covalent bond, CH2, and CH2CH2; Z = covalent bond, CH2, and CH2CH2, provided that when Y is CH2CH2, then Z is a covalent bond and further provided that when Z is CH2CH2, then Y is a covalent bond. R1 = optionally substituted phthalazin-1-yl, pyridin-3-yl, pyrazinyl, pyrimidin-5-yl, pyridazin-3-yl, quinolin-3-yl, thieno[3,2-b]pyridin-2-yl, furano[3,2-b]pyridin-2-yl, thieno[3,2-b]pyridin-3-yl, furano[3,2-b]pyridin-3-yl, furano[3,2-b]pyridin-6-yl, thieno[3,2-b]pyridin-6-yl, furano[2,3-b]pyridin-5-yl, thieno[2,3-b]pyridin-5-yl, isothiazol-5-yl, isoxazol-5-yl. R9 = H, alkoxycarbonyl, alkyl, amino, aminoalkyl, aminocarbonylalkyl, benzyloxycarbonyl, cyanoalkyl, dihydro-3-pyridinylcarbonyl, hydroxy, hydroxyalkyl, and phenoxycarbonyl. Values are reported for nicotinic acetylcholine receptor binding potencies and effectiveness of nicotinic acetylcholine receptor ligands as analgesic agents and in the formalin test for some of the claimed compds. Ninety-six example prepns. are given but the methods of preparation are not claimed. The crystal and mol. structures of (3aS,6aS)-5-[(4-nitrophenyl)sulfonyl]-1-((1R)-1-phenylethyl)octahydropyrrolo[3,4-b]pyrrole and tert-Bu (3S,4S)-4-(hydroxymethyl)-3-[((1S)-1-phenylethyl)amino]-1-piperidinecarboxylate were determined by x-ray crystallog.

L2 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:246314 CAPLUS
DN 135:76756
TI Design and synthesis of ether analogues as potent and selective M2 muscarinic receptor antagonists
AU Wang, Y.; Chackalamannil, S.; Chang, W.; Greenlee, W.; Ruperto, V.; Duffy, R. A.; McQuade, R.; Lachowicz, J. E.
CS Schering-Plough Research Institute, Kenilworth, NJ, 07033, USA
SO Bioorganic & Medicinal Chemistry Letters (2001), 11(7), 891-894
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 135:76756
AB Selective M2 muscarinic antagonists, 4-{4-[4-(arylsulfonyl) phenoxy]piperidin-1-yl}piperidines, which replace a metabolically labile styrenyl moiety of a prototypical M2 antagonist with an ether linkage, were synthesized. A detailed SAR study in this class of compds. yielded highly active compds. that showed M2 Ki values of <1.0 nM and >100-fold selectivity against M1, M3, and M5 receptors.
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1997:458563 CAPLUS
DN 127:171470
TI Antinociceptive profile of 3-α-tropanyl-(2-Cl)-acid phenoxybutyrate (SM-21): a novel analgesic with a presynaptic cholinergic mechanism of action
AU Ghelardini, Carla; Galeotti, Nicoletta; Gualtieri, Fulvio; Bellucci, Cristina; Manetti, Dina; Giotti, Alberto; Malmberg-Aiello, Petra; Galli, Alessandro; Bartolini, Alessandro
CS Dep. of Pharmacology and Dep. of Pharmaceutical Sciences, University of Fluorence, Fluorence, I-50134, Italy

SO Journal of Pharmacology and Experimental Therapeutics (1997), 282(1), 430-439
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
AB The antinociceptive effect of (±)-3-α-tropanyl-(2-Cl)-acid phenoxybutyrate (SM-21) (10-40 mg kg-1 s.c., 10-30 mg kg-1 i.p., 20-60 mg kg-1 p.o., 3-20 mg kg-1 i.v. and 5-20 μg per mouse i.c.v.) was examined in rodents and guinea pigs by using the hot-plate, abdominal constriction, tail-flick and paw-pressure tests. The antinociception produced by (±)-SM-21 was prevented by atropine, pirenzepine and hemicholinium-3 but not by quinpirole, R-(α)-methylhistamine, [1-[[2-(methylsulfonyl)amino]ethyl]-4-piperidinyl]methyl-5-fluoro-2-methoxy-1H-indole-3-carboxylate hydrochloride, N6-cyclopentyladenosine, 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine hydrobromide, naloxone, 3-aminopropyl-diethoxy-methyl-phosphinic acid or reserpine. On the basis of the above data, it can be postulated that (±)-SM-21 exerted an antinociceptive effect mediated by a central potentiation of cholinergic transmission. Affinity profiles of (±)-SM-21 for muscarinic receptor subtypes, determined by functional studies (rabbit vas deferens for M1, guinea pig atrium for M2, guinea pig ileum for M3 and immature guinea pig uterus for putative M4) have shown a selectivity ratio M2/M1 of 4.6 that, although very low, might be responsible for the antinociception induced by (±)-SM-21 through an increase in ACh extracellular levels. In the antinociceptive dose range, (±)-SM-21 did not impair mouse performance evaluated by the rota-rod and hole-broad tests.

L2 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1993:618003 CAPLUS
DN 119:218003
TI Selective inactivation of muscarinic M2 and M3 receptors in guinea pig ileum and atria in vitro
AU Eglen, R. M.; Harris, G. C.
CS Inst. Pharmacol., Syntex Discovery Res., Palo Alto, CA, 94304, USA
SO British Journal of Pharmacology (1993), 109(4), 946-52
CODEN: BJPCBM; ISSN: 0007-1188
DT Journal
LA English
AB The role of muscarinic M2 and M3 receptors in ileal smooth muscle has been evaluated by use of selective receptor alkylation. The alkylating agents, 4-diphenylacetoxy-N-(2-chloroethyl)-piperidine (4-DAMP mustard) was studied for effects against (+)-cis-dioxolane, at muscarinic M2 and M3 receptors in guinea-pig atria or ileum, resp. 4-DAMP mustard, at 100 nM, resulted in a large dextral shift (197 fold) and depression in maximum In atria there was a smaller dextral shift (14 fold) but no depression in maximum The muscarinic antagonists, atropine (non-selective), methoctramine (M2-selective) and para-fluorohexahydro-siladiphenidol (pFHHSiD; M3 selective) were studied in protection studies against alkylation by phenoxybenzamine. Washout studies following equilibration of the tissues with atropine (30 nM), methoctramine (0.3 μM) or pFHHSiD (3 μM), showed the compds. to be reversible. No temporal changes in sensitivity to (+)-cis-dioxolane were observed Exposure, for 20 min, of atria and ileum to phenoxybenzamine (3 and 10 μM resp.) caused dextral shifts and depressions in the maximum of the concentration-response curve to (+)-cis-dioxolane.
These effects were inhibited by prior equilibration with atropine (30 nM) and methoctramine (0.1 μM) in atria or atropine (30 nM) and pFHHSiD (3 μM) in ileum. Similar results in ileum were obtained when pilocarpine was used as the agonist. These data were consistent with

muscarinic M2 receptors mediating responses in atria and M3 receptors mediating responses in ileum. No evidence was provided for a direct role of muscarinic M2 receptors in ileal contraction. It is concluded that receptor protection by reversible antagonists for muscarinic M2 or M3 receptors provides a means to isolate pharmacol. a single subtype in a tissue possessing heterogeneous populations. This technique may prove useful in defining the role of the resp. subtypes in smooth muscle contraction.

L2 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1957:73023 CAPLUS
DN 51:73023
OREF 51:13189f-i,13190a-f
TI The pharmacological action exercised by serotonin on several isolated organs (intestine and auricle)
AU Levy, Jeanne; Michel-Ber, Estera
CS Inst. Fournier, Paris
SO Journal de Physiologie (Paris, 1946-1992) (1956), 48, 1051-84
CODEN: JOPHAN; ISSN: 0021-7948
DT Journal
LA Unavailable
AB cf. C.A. 50, 15901ad; 17296i; 51, 5277h. Serotonin (I, 5 + 10-8 - 7.5 + 10-6M) exercises a spasmogenic action on isolated rat duodenum. This action is not modified by treatment with the following agents for 1-2 min. prior to I: atropine sulfate (II, 5-25 + 10-9M with I at 5-10 + 10-6M), pentamethonium bromide (III, 5-10 + 10-6M), hexamethonium bromide (IV, 5-10 + 10-6M), nicotine -HCl (V, 1-2.5 + 10-6M), promethazine (Phenergan, VI, 5 + 10-8M). The spasmogenic action is diminished by: papaverine-HCl (VII, 1.25-5 + 10-6M), II (5-25 + 10-9M with I at 5 + 10-7M), 2-piperidinoethyl[bicyclohexyl]-1-carboxylate (Dihexyverine, VIII, 5-10 + 10-8M), V (2.5 + 10-5M, feeble), VI (1.25 + 10-7M), eserine-1/2 H2SO4 (IX, 5-12.5 + 10-8M). In 50% of the expts. N,N-diethyllysergamide (X, 2.5-25 + 10-8M) diminishes the spasmogenic action; in the other expts. a biphasic action (depression followed by contraction) is observed The biphasic action is also sometimes caused by VII (1.25-2.5 + 10-7M) followed by I (1.25 + 10-6M) and is regularly observed (90% of cases) using II (1.25-2.5 + 10-6M), X (5-25 + 10-8M), and then I (2.5 + 10-6M). The depressive phase is augmented by ergotamine tartrate (2.5-25 + 10-7M) and suppressed by yohimbine-HCl (XI, 1-2.5 + 10-5M), Ilidar (5-7.5 + 10-6M), V (2.5-7.5 + 10-5M), phenoxycholine iodide (2.5-5 + 10-4M), Me4NBr (XII, 2.5 + 10-3M), and VI (1.25 + 10-6). The biphasic action is not affected by IV (1-10 + 10-6M), XII (2.5 + 10-4M), Et4NBr (2.5-5 + 10-4M), procaine-HCl (XIII, 1.25-10 + 10-6M), or VI (1.25-5 + 10-7). IX (5 + 10-8M) transforms the biphasic effect into a long depressive action sometimes preceded by a short spasmogenic phase. I (7.5 + 10-5M) given before V (3.75 + 10-6M) does not affect the action of the latter. Adenosinetriphosphate (5-12.5 + 10-7M) produces a similar biphasic action which is not modified by prior treatment with II (1.25 + 10-8M), VIII (2.5-25 + 10-7M), VII (1.25-5 + 10-6M), IV (5-10 + 10-6M), XIII (5 + 10-5M), or IX (5-12.5 + 10-7M). The effect is sometimes exaggerated by XI (1-1.5 + 10-5M) or V (7.5 + 10-5M, depressive phase). The spasmogenic action on isolated rat ileum caused by I (2.5-20 + 10-7M) is not affected by II (5 + 10-9 - 7.5 + 10-7M) but is converted to a depressive action by IX (6.25 + 10-8M). On the isolated guinea pig ileum I (1.25-25 + 10-7M) exerts a short spasmogenic action which is sometimes followed by a depressive effect. The contraction is not affected by IV (5-10 + 10-6M), XIII (5 ° 10-6M), or VI (7.5 + 10-9M) but is diminished or suppressed by X (5-50 + 10-9M)

or II (1.25 + 10-8M). The biphasic effect of I on guinea pig ileum is obtained more regularly in the presence of IX (2.5-5 + 10-8M). XI (5 + 10-6M) or IV (5 + 10-6M) suppress the depressive phase of the action. I (2.5-10 + 10-6M) exercises in 50% of the expts. a pos. inotropic and chronotropic effect on the isolated right auricle of the rabbit. In the other cases the pos. effect is preceded by a short neg. inotropic and chronotropic phase. Modification of this action by other agents placed in contact with the auricle for 5 min. prior to I unless otherwise noted is as follows: The depressive action is reinforced by IX (1.25 + 10-6M, 15 min.), suppressed by II (5 + 10-7M, 1-2 min.) and not affected by III or IV (7.5 + 10-6M). The pos. inotropic and chronotropic effect is diminished or suppressed by d-tubocurarine chloride (XIV, 7.5 + 10-6M), X (1.25-25 + 10-6M), ephedrine-HCl (1.25 + 10-5M), VI (2.5-10 + 10-7M), or XIII (1.25 + 10-5M). The pos. action is not affected by II (2.5 + 10-7M), III (7.5-50 + 10-6M), IV (7.5-10 + 10-6M), VI (1.25-5 + 10-7M), IX (1.25-3.75 + 10-6M), X (2.5 + 10-7M), XIII (2.5 + 10-6M), Flaxedil (2.5-25 + 10-5M), or hexamethylenebiscarbaminoylcholine iodide (5-25 + 10-6M). I is ineffective immediately after the effects from treatment with V (2.5 + 10-5M); acetylcholine chloride (1.25 + 10-4M, 1 min.) - II (1.25 + 10-5M) or Me4NI (2.5 + 10-4M, 1 min.) - II (1.25 + 10-5M) have subsided. After administration of I (5 + 10-5M, 15 min.), V (6.25 + 10-7M) is ineffective while adrenaline-HCl retains its activity. The expts. were repeated using guinea-pig auricle with similar results except that VI, X, and XIV did not affect the stimulative action of I. The physiol. mechanisms of the effects are discussed.

L2 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1954:53956 CAPLUS
DN 48:53956
OREF 48:9551b-f
TI Mechanism of action of various ganglionic excitants on the isolated rodent intestine
AU Levy, Jeanne; Michel-Ber, Estera; Cafiot, Micheline
CS Fac. med., Paris
SO Journal de Physiologie (Paris, 1946-1992) (1953), 45, 687-722
CODEN: JOPHAN; ISSN: 0021-7948
DT Journal
LA Unavailable
AB The cholinergic nature of the contractile action of ganglionic excitants was shown by the following: Atropine (I) suppressed or diminished the spasmodic action induced by nicotine (II) and phenoxycholine iodide (III) at levels which suppressed the action of acetylcholine (IV) on the same surviving fragment of guinea-pig ileum. I diminished the spasmodic action of III and increased the depressive phase of its action on the isolated rat duodenum. The adrenergic action was shown by the suppression of the depressive action of II and III on rat duodenum by the adrenolytics, yohimbine and ergotamine tartrate; in concns. that inhibited the action of noradrenaline. The suppression by tetraethylammonium (V) and hexamethonium bromide (VI) of the spasmodic action induced by II and III on isolated guinea-pig ileum was seen at doses that had no influence on the action of IV and therefore suggests a ganglionic origin for the effects of II and III. The contractile action of II and III on rat and guinea-pig ileum is increased by doses of eserine (VII) which have no effect on the action of IV. The contractile action of II on rat duodenum is increased by doses of VII, neostigmine (VIII), and difluophosphate (IX). This is interpreted as evidence that the action of II and III is partly by way of cholinergic preganglionic fibers. V and VI suppress the depressive action of II and III on rat duodenum, while VII, VIII, and IX increase this action. This

is interpreted as evidence that II and III exert their depressive action by way of cholinergic preganglionic fibers to adrenergic postganglionics. A comparison of several ganglionic excitants led to the following classification of activities: cholinergic action, piperidine (X) > II > III > N-furfurylpiperidine (XI) = N-benzoylpiperidine (XII); adrenergic action, XII = XI > III > II > X. Comparison of the organs studied gave the following series: cholinergic reactivity, guinea-pig ileum > rabbit jejunum = guinea-pig duodenum = rat ileum > rat duodenum; adrenergic activity, rat duodenum > rat ileum > guinea-pig ileum, duodenum = rabbit jejunum.

L2 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1930:10314 CAPLUS
DN 24:10314
OREF 24:1157d-g
TI Further studies on the relation of heterocyclic compounds to the autonomic nervous system
AU Hunt, Reid; Renshaw, R. R.
SO J. Pharmacol. (1929), 37, 177-91
DT Journal
LA Unavailable
AB The following compds. were studied: (1) quaternary compds. of quinoline and its homologs (ethiodides of quinoline, quinaldine, lepidine, 6-methylquinoline, 2,4-dimethylquinoline and 2,6-dimethylquinoline; (2) esters of nicotinic and picolinic acids, and amides, and substituted amides of these acids and of their N-methyl compds. (α-carbophenoxy- and β-carbophenoxypyridinium bromides, methyl (β-carbophenoxy)-, methyl (β-carbamido)-, methyl (β-phenylcarbamido)-, methyl (β-ethylphenylcarbamido)- and methyl (α-phenylcarbamido)-2, methyl (β-carboxypiperidino)- and methyl (β-acetamino)- pyridinium iodides, β-phenylcarbamido pyridinium bromide and N-carboxymethyl α-methyl pyridinium sulfate, β-acetamino- pyridine; (3) ethers of pyridinium, piperidinium and pyrrolidinium compds. (β- phenoxyethyl-N-pyridinium bromide, β- phenoxyethyl-N-methylpyrrolidinium iodide, β- phenoxyethyl-N-methyl-piperidinium iodide and β- phenoxyethyl-N-ethylpiperedinium bromide). Members of groups 1 and 2 had little or no muscarine or nicotine actions. The members of group 3 had no muscarine action. β- Phenoxyethyl-N-methylpyrrolidinium iodide had a stimulating and a paralyzing (large doses) nicotine action, while the other compds. did not have such action.

L2 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1929:25297 CAPLUS
DN 23:25297
OREF 23:3022i,3023a-f
TI Some effects of derivatives of betaine amide and of choline ethers on the Autonomic nervous system
AU Hunt, Reid; Renshaw, R. R.
CS Harvard Med. School;N. Y. Univ.
SO J. Pharmacol. (1929), 35, 99-128
DT Journal
LA Unavailable
AB The effect on blood pressure of cats, either anesthetized or with brain and upper cord destroyed, and the toxicity for mice, of the following compds. is reported: betaine chloride, carbamylmethyltrimethylammoniumchloride, N-methylcarbamylmethyltrimethylammonium chloride, N-ethylcarbamylmethyltrimethylammonium chloride, N-propylcarbamylmethyltrimethylammonium chloride, N-butylcarbamylmethyltrimethylammonium chloride, N-phenylcarbamylmethyltrimethylammonium chloride, N-p-

hydroxyphenylcarbamylmethyltrimethylammonium chloride, N-o-methoxyphenylcarbamylmethyltrimethylammonium chloride, N-p-methoxyphenylcarbamylmethyltrimetbylammonium chloride, N-o-ethoxyphenylcarbamylmethyltrimethylammonium chloride, N-p-ethoxyphenylcarbamylmethyltrimethylammonium chloride, N-p-tolylcarbamylmethyltrimethylammonium chloride, N-α-naphthylcarbamylmethyltrimethylammonium chloride, N-β-naphthylcarbamylmethyltrimethylammonium chloride, carbpiperidinotrimethylammonium chloride, carbureidomethyltrimethylammoniu m bromide, carbphenylureidomethyltrimethylammonium bromide, phenoxyethyltrimethylammonium bromide, phenoxypropyltrimethylammonium bromide, dimethylphosphatoethyltrimethylammonium chloride, choline sulfuric acid ester, N-phenylcarbamylmethyltri-i-amylammonium bromide. When a phenyl group was substituted in the amide group of betaine amide (carbamylmethyltrimethylammonium chloride to N-phenylcarbamylmethvltrimethylammonium chloride) the muscarine action (fall in blood pressure which was prevented by a small dose of atropine and which occurred after a large paralyzing dose of nicotine) diminished, and the stimulating nicotine action (rise in blood pressure in a pithed and atropinized animal, which was prevented by a large dose of nicotine) increased. Substitution of a phenyl group in betaine ethyl ester or in choline also abolished muscarine action and in the latter compound increased the blood-pressure-raising action. When the side chain was lengthened (phenoxyethyltrimethylammonium bromide to phenoxypropyltrimethylammonium bromide) nicotine action diminished. When a substituted phenyl group (as hydroxypheny), methoxyphenyl or etboxyphenyl) was introduced (N-phenylcarbamylmethyltrimethylammonium chloride to N-p-hydroxyphenylcarbamylmethyltrimethylammonium chloride) the nicotine action was diminished or abolished, but muscarine action did not return. Compds. with substituted phenyl groups were more toxic than the phenyl derivative When the H of the amide group in betaine amide was substituted by a Me (and to a less extent by an Et) group, or by a piperidino or carbureido group, muscarine action increased, while if the Me group was substituted in the methylene group of the esters of betaine the muscarine action diminished. Toxicity was parallel to increase in muscarine action. When a Ph group was substituted in the methylene group of betaine esters the muscarine action was depressed, but the stimulating nicotine action was not increased as it was by substituting the Ph group in the amide group of betaine amide. Most of the compds. had a paralyzing nicotine action.